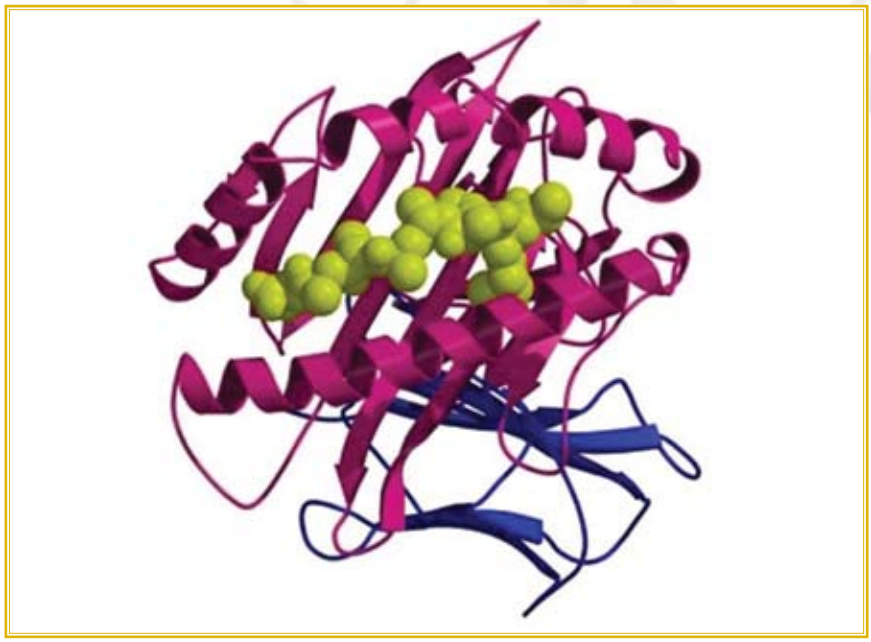
High Marks for Destruction

Genetic variations boost HIV-killing immune response to slow disease progression.

Throughout the history of the AIDS epidemic, a few lucky people have avoided full-blown onset of the disease despite being exposed to HIV. Host genetic variation appears to play a major role in slowing disease progression in HIV-infected patients. In particular, individuals with naturally occurring variants of certain human leukocyte antigen (HLA) genes appear to take years longer to develop AIDS and die of complications of the disease. HLA genes encode cell surface proteins that present antigen—in this case, from HIV—to lymphocytes for destruction.

In a paper published in the November 22, 2009 issue of *Nature Genetics*, a team of researchers led by Mary Carrington, Ph.D., Head of the Immunogenetics Section at the Laboratory of Experimental Immunology at CCR, demonstrated that high levels of HLA cell surface protein HLA-C are associated with lower viral loads and slower progression of HIV to AIDS.

The researchers looked at variants in a region known to associate with levels of HLA-C gene expression and also to have one of the strongest genome-wide associations with the level of HIV in the blood during early infection: a region located 35 kilobases upstream (-35) of HLA-C. They genotyped nearly 1,700 HIV-positive individuals to determine which -35 variant they carried. They found that individuals with a variant called -35TT expressed HLA-C cell surface protein at low levels compared to individuals with a variant called -35CC. Furthermore, individuals with the -35CC variant—and therefore greater cell surface expression of HLA-C—had much lower levels of virus in the blood, better protection against HIV, and slower progression to AIDS.



(Image: M. Carrington)

The HLA molecule (magenta) presents a pathogen peptide (green spheres) to the immune system.

The fact that the -35CC variant correlates with high HLA-C protein levels and lower levels of virus present in blood after HIV infection suggests that the genetic variation makes it easier for the immune system to kill cells infected with the virus. "If you have more HLA-C on the cell surface, the immune system's T cells are going to recognize that infected cell much better than if the cell had low levels of HLA-C expression," said Dr. Carrington. "The ones with high expression are going to make it very clear to the immune system that this cell is infected and needs to be destroyed."

A better understanding of this type of genetic variation could help in the development of vaccine- or immune-based therapies that could delay or even prevent the development of AIDS. But the researchers will first need to elucidate the mechanism underlying their observations. "So what we're working on now is to figure out what is directly causing the difference in level of expression of HLA-C," said Dr. Carrington. "The next step is to determine whether that mechanism could be manipulated in a way that we can turn low expression HLA-C alleles into high expression HLA-C alleles. But until we understand the mechanism, we have no way of knowing how to approach that question."

To learn more about Dr. Carrington's research, please visit her CCR Web site at ***http://ccr.cancer.gov/staff/staff.asp?Name=carrington****.*